XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. CO32

Monoclonal Gammopathies & Multiple Myeloma

ARQ531 TARGETS MAPK–S6K1 SIGNALING AND SYNERGIZES WITH LENALIDOMIDE IN RAS-MUTANT AND WILD-TYPE MULTIPLE MYELOMA

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Introduction: Multiple myeloma (MM) is a plasma cell malignancy driven by dysregulated kinase signaling, including aberrant MAPK activation frequently associated with oncogenic RAS mutations. ARQ531 is an orally available multi-kinase inhibitor that we previously characterized in leukemia, where it demonstrated potent anti-tumor activity through broad kinase inhibition and MYC transcriptional reprogramming. To elucidate its mechanism of action in MM, we integrated phosphoproteomic and functional analyses to delineate signaling vulnerabilities modulated by ARQ531 and evaluated its therapeutic potential in combination with standard anti-MM agents.

Methods: Global and phospho-TMT quantitative proteomics were performed on ARQ531-treated MM cells to identify drug-modulated signaling pathways. Kinase–Substrate Enrichment Analysis (KSEA) defined key regulatory nodes of drug response. Functional and combination studies were conducted in MM cell lines, including RAS-mutant models, patient-derived plasma cells, and murine xenografts. Bioinformatic analyses of public MM datasets corroborated experimental findings.

Results: Phosphoproteomic profiling revealed that ARQ531 profoundly remodels the MM kinome, strongly inhibiting MAPK signaling and the S6K1 axis, identified by KSEA as a critical functional hubs mediating drug efficacy. MM cells with acquired tolerance to ARQ531 maintained activation of these cascades, confirming their mechanistic relevance. RAS-mutant MM models—both cell lines and patient-derived plasma cells—displayed enhanced sensitivity to ARQ531, and analysis of the CoMMpass dataset revealed that RAS-mutant patients with an *ARQ531-treated–like* transcriptional signature exhibited improved progression-free and overall survival. Notably, since the RAS–S6K1 axis is implicated in lenalidomide resistance, ARQ531, by co-targeting both pathways, exhibited strong synergy with lenalidomide, enhancing cytotoxicity in vitro, ex vivo, and in vivo. Importantly, this cooperative effect was also observed in RAS–wild-type models, indicating broader therapeutic applicability.

Conclusions: Integrative phosphoproteomic and functional analyses identify the MAPK–S6K1 axis as a key signaling vulnerability targeted by ARQ531 in MM across both RAS–wild--type and RAS-mutant contexts. The strong synergy with lenalidomide supports the development of ARQ531-based combination strategies to exploit kinase signaling dependencies and overcome therapeutic resistance in multiple myeloma.